transformation and/or fusion to myeloma cells. Total cell RNA is isolated, then mRNA encoding the antibody is isolated from the total RNA. cDNA is synthesized and then inserted into a cloning vector. A host cell is transformed to get a cDNA library, which then is screened for cDNA encoding the constant and variable regions of the heavy and light chains of the desired antibody. The cloned cDNA encoding the heavy and light chains of the antibody is inserted into an expression vector under the control of expression signals. A host cell is transfected with the expression vector and then cultured under antibody-producing conditions and the antibody so produced is isolated.

Applicants note with appreciation that the rejection of claims 1-14 under 35 U.S.C. § 101 and one of the rejections of claims 1-14 under 35 U.S.C. § 112, first paragraph, set forth in the first Office Action, have been withdrawn in this most recent Office Action.

The examiner has maintained a second rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph, on the basis that the claimed invention is not enabling for the use of the claimed invention as a diagnostic aid or as a therapeutic agent. The examiner asserted that the specification fails to adequately teach how to use the antibodies of the invention as diagnostic aids. This rejection is traversed.

Enclosed with this Amendment is a declaration by Dr. Alan Lewis, one of the inventors of the present invention.[1] Dr.

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[1] An unsigned copy of this declaration is submitted herewith. The signed original will be submitted as soon as it is received from Dr. Lewis.

Lewis explains in his declaration that persons of ordinary skill in the art would be able to use the antibodies of the present invention as diagnostic agents without the need for detailed instructions in the application.

The earlier rejection of claims 1-2, 4-5, 7-10 and 12-14 under 35 U.S.C. §012 (b) as anticipated by Gillies et al. has been maintained. Gillies et al. were said to teach methods for the production of human antibodies from cDNA libraries. The examiner noted that Applicants had argued in their last response that their specification was distinguishable from the teachings of this references in that the specification teaches the cloning and insertion of the entire cDNA sequence encoding the heavy and light chain of immunoglobulin molecules into a vector. He then asserted that no such limitation is present in the claims of the application. He further asserted that even if such a limitation were present, the claimed invention would be obvious under 35 U.S.C. § 103 as the Applicants' specification indicates that methods of inserting complete cDNA sequences into expression vectors were known prior to Applicants' invention. He cited page 14, second paragraph, of the specification in support of this contention. This rejection is traversed.

Applicants have amended the claims to specify that cDNA sequences encoding the entire constant and variable regions of the light and heavy chains of the desired antibodies are used. Applicants respectfully submit that this amendment clearly obviates the § 102 rejection.

With regard to the § 103 rejection, the cited paragraph of the Applicants' specification provides that heavy and light chain cDNA can be transfected in a single vector as taught in PCT application WO87/04462 or co-transfected in two vectors as subsequently taught in Applicants' invention. The 04462 application discloses vectors containing a recombinant DNA sequence encoding the complete amino acid sequence of a glutamine synthetase which are useful as expression vectors. More specifically, the application teaches a method for co-amplifying a recombinant DNA sequence which encodes a desired protein by either (1) co-transforming a host cell with a vector containing a DNA sequence encoding a glutamine synthetase and a vector comprising a recombinant DNA sequence which encodes the desired protein or (2) transforming a host cell with a vector containing a DNA sequence encoding a glutamine synthetase and which further contains a recombinant DNA sequence encoding the desired protein. Expression of the GS gene provides transformant cells with a dominant selectable marker; cells transformed with the two vectors have resistance to GS inhibitors. The focus of the application is on providing the recombinant DNA encoding the complete amino acid sequence of a glutamine synthetase and its use in the construction of expression vectors. There is very little discussion in the application about the DNA encoding the desired protein. In the paragraph bridging pages 9-10 of the application, the applicants state that this DNA can encode tissue plasminogen activator (tPA) or "any other protein, such as

immunoglobulin polypeptides (IGs), human growth hormone (hGH) or tissue inhibitor of metalloproteinases (TIMP)." There is no other discussion about the DNA encoding the protein of interest. Contrary to the examiner's assertion, this reference does not provide an enabling disclosure that antibodies can be produced by inserting the cDNA encoding both the constant and variable regions of the antibody light and heavy chains into an expression vector under the control of expression signals, transfecting a host cell with the vector and then culturing the host under protein-producing conditions. There is no discussion in the reference at all as to whether DNA encoding variable and constant regions of the light or heavy chain of an antibody can be provided completely by cDNA, by genomic DNA or by a combination of the two. A person of ordinary skill in the art who had read both the Gillies reference and the 04462 application would be left with the conclusion that if one wished to produce a recombinant antibody, one would use cDNA encoding the variable region and a portion of the constant region and genomic DNA of the same Ig class to provide the remainder of the DNA encoding the constant region. Thus, claims 1-2, 4-5, 7-10 and 12-16 are not rendered obvious by the two references.

Claims 3 and 6 stand rejected under 35 U.S.C. § 103 as unpatentable over Gillies et al. in view of Foung et al. and Ehrlich et al. In maintaining this rejection, the examiner reiterated his earlier comments regarding the Gillies reference and PCT WO/04462. This rejection is traversed.

Applicants respectfully submit that their comments above regarding the deficiencies of the Gillies reference and the 04462 application are equally valid in connection with the rejection of claims 3 and 6. Gillies et al. teaches using a combination of cDNA and genomic DNA to provide a DNA sequence encoding the entire constant region of an antibody. In contrast to this teaching, Applicants use cDNA encoding the entire constant region and the entire variable region. The 04462 reference, as explained above, does not teach that using cDNA sequences encoding the entire heavy and light chains of an antibody was known prior to the Applicants' present invention. The two secondary references do not overcome the deficiencies of the Gillies et al. paper or the 04462 application. Neither Foung et al. nor Ehrlich et al. teach or suggest any method for producing recombinant antibodies, much less that a recombinant antibody could be produced by obtaining the cDNA encoding the entire constant and variable regions of each of the heavy and light chain of the antibody, inserting the cDNA into an expression vector under the control of expression signals, transfecting a cell with the expression vector and then culturing the cell under antibody-producing conditions.

Claim 11 stands rejected under 35 U.S.C. § 103 as obvious over Gillies et al. in view of Larrick et al. Again, the examiner reiterated his comments regarding Gillies and PCT application 04462 as his reason for maintaining this rejection.